

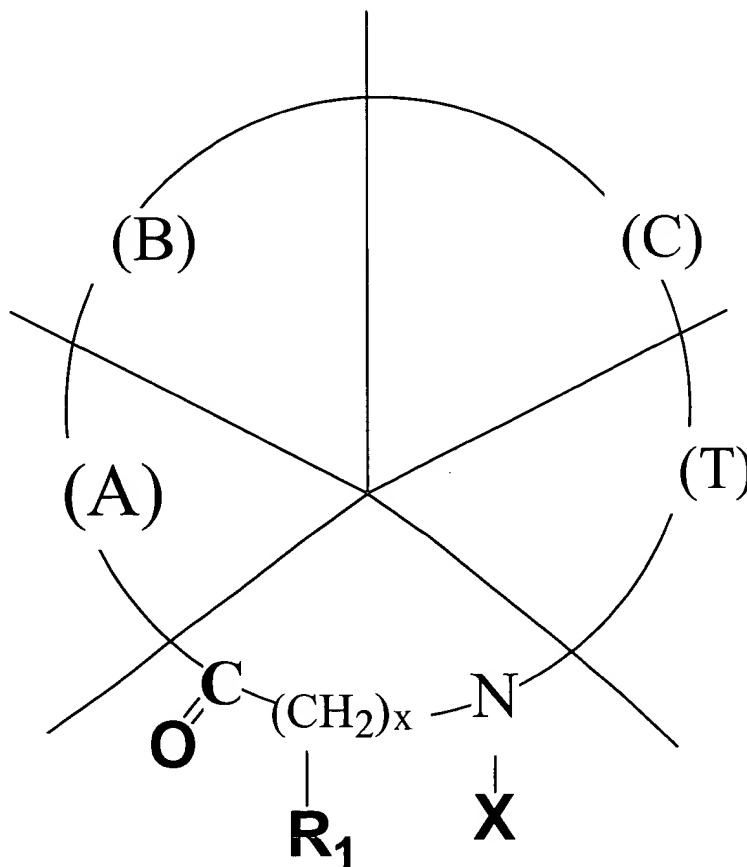
*B1*  
*cancel* d) carrying out a macrocyclization of the unprotected product obtained in step c) and a cleavage if the preparing and coupling steps (a), (b) were carried out in the solid phase in order to obtain the requested compound of the formula (I).

**In the Claims:**

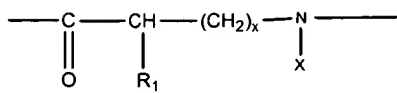
Please cancel claims 1-10.

Please add new claims 24-33 as follows:

-- 24. (new) A macrocyclic compound of the formula (I)



- where part (A) is a  $\begin{array}{c} \text{---C---CH---(CH}_2\text{)}_y\text{---NH---} \\ \parallel \quad | \\ \text{O} \quad \text{R}_2 \end{array}$  bivalent radical  
having its -NH- group linked to the carbonyl group of part



a  $\text{---(CH}_2\text{)}_y\text{---}$  bivalent radical, or a covalent bond;

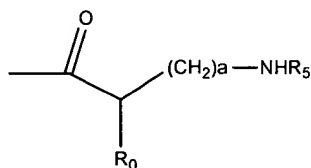
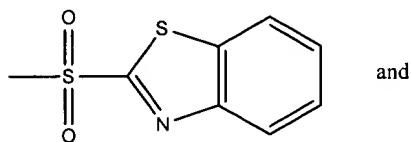
-where part (B) is a  $\begin{array}{c} \text{---C---CH---(CH}_2\text{)}_z\text{---NH---} \\ \parallel \quad | \\ \text{O} \quad \text{R}_3 \end{array}$  bivalent radical having its  $\text{---NH---}$  group linked to part (A), a  $\text{---(CH}_2\text{)}_z\text{---}$  bivalent radical, or a covalent bond;

-where part (C) is a  $\begin{array}{c} \text{---C---CH---(CH}_2\text{)}_z\text{---NH---} \\ \parallel \quad | \\ \text{O} \quad \text{R}_4 \end{array}$  bivalent radical having its  $\text{---NH---}$  group

linked to part (B) a  $\text{---(CH}_2\text{)}_t\text{---}$  bivalent radical, or a covalent bond;

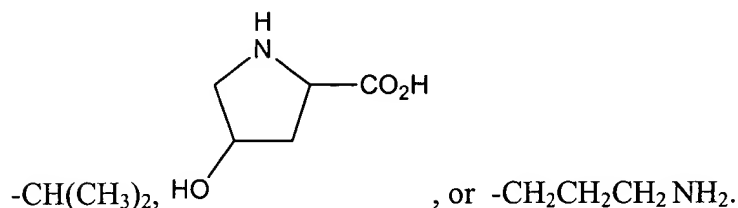
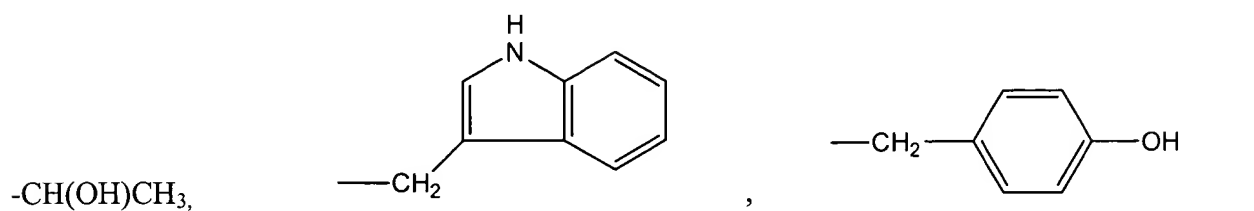
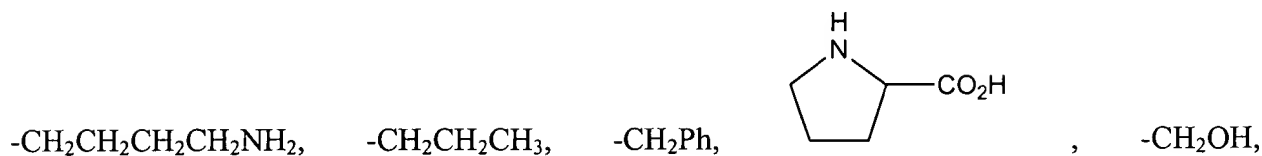
- where part (T) is a  $\text{---Y---L---Z---}$  radical; and

- where X is a monovalent group selected from the group consisting of:  $\text{---SO}_2\text{---Ar}$ ,  $\text{---SO}_2\text{---CH}_3$ ,  $\text{---SO}_2\text{---CF}_3$ ,  $\text{---H}$ ,  $\text{---COH}$ ,  $\text{---CO---CH}_3$ ,  $\text{---CO---Ar}$ ,  $\text{---CO---R}$ ,  $\text{CO---NHR}$ ,  $\text{---CO---NHAr}$ ,  $\text{---CO---O---tBu}$ ,  $\text{---CO---O---CH}_2\text{---Ar}$



- Ar being an aromatic group, substituted aromatic group or a heteroaromatic group,
- a being an integer selected from the group consisting of 0, 1 and 2,
- R being a monovalent group  $\text{---(CH}_2\text{)}_n\text{---CH}_3$  or  $\text{---(CH}_2\text{)}_n\text{---Ar}$  with n being an integer from 1 to 16.

- $R_0, R_1, R_2, R_3$  and  $R_4$  are, independently,  $-\text{CH}_3$ ,  $-\text{CH}_2\text{CH}_2\text{CH}_2\text{NHC}(=\text{NH})\text{NH}_2$ ,  
 $-\text{CH}_2\text{C}(=\text{O})\text{NH}_2$ ,  $-\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{SH}$ ,  $-\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$ ,  $-\text{CH}_2\text{CH}_2\text{C}(=\text{O})\text{NH}_2$ ,



proline and hydroxyproline may be used at positions 0, 2 and 3; and 1 when X is CO,

$R_5$  being a monovalent radical selected from the group consisting of  $-\text{H}$ ,  $-\text{SO}_2\text{CH}_3$ ,  $-\text{SO}_2\text{CF}_3$ ,  
 $-\text{CHO}$ ,  $-\text{COCH}_3$ ,  $-\text{CO-Ar}$ ,  $-\text{CO-R}$ ,  $-\text{CO-NHR}$ ,  $-\text{CONHAr}$ ,  $-\text{COO-tBu}$  and  $-\text{COO-CH}_2\text{-Ar}$ , wherein  
 R and Ar are depicted as previously.

- where Y is a bivalent group  $-\text{CH}_2-$  or  $-\text{CO}-$ ;

- where Z is a bivalent group  $-\text{NH}-$  or  $\text{O}-$ ;

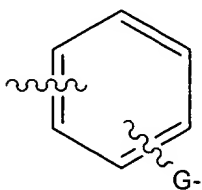
- wherein x, y, z and t are integers each independently selected from the group consisting of 0, 1,  
 and 2;

- wherein L is a bivalent radical selected from the group consisting of:

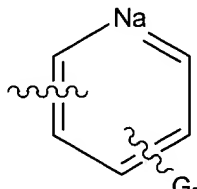
$-(CH_2)_d-A-(CH_2)_j-B-(CH_2)_e-$ , d being an integer from 0 to 5, e being an integer from 1 to 5, j being an integer from 0 to 5, when j is 0, A and/or B is present, with A and B being independently selected from the group consisting of: -O-, -NH-, -NR- wherein R is defined as above, -S-, -CO-, -SO-, -CO-O-, -O-CO-, -CO-NH-, -NH-CO-, -SO<sub>2</sub>-NH-, -NH-SO<sub>2</sub>-,

$—CH=CH—$  with this configuration Z or E,

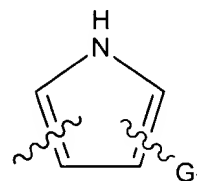
$—C\equiv C—$ ,



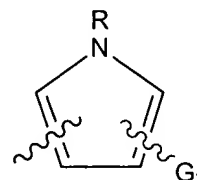
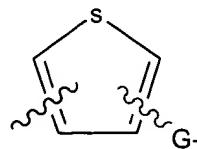
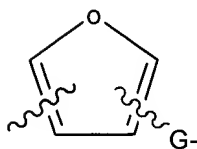
substitution  
1,2; 1,3; 1,4



substitution  
2,3; 2,4; 2,5;  
2,6; 3,4; 3,5;



substitution  
1,2; 1,3; 2,3;  
2,4; 2,5; 3,4

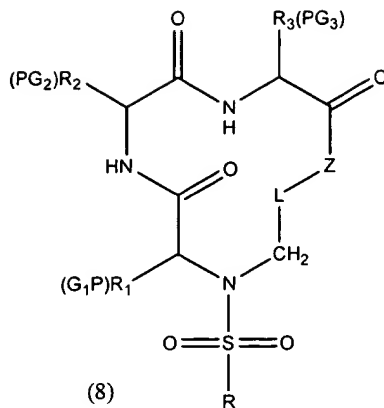


substitution  
2,3; 2,4; 2,5; 3,4

R is defined as above and G is either a covalent bond or a bivalent radical selected from the group consisting of -O-, -NH-, -NR- wherein R is again defined above, -S-  $—CH=CH—$  with the configuration Z or E, and  $—C\equiv C—$ .

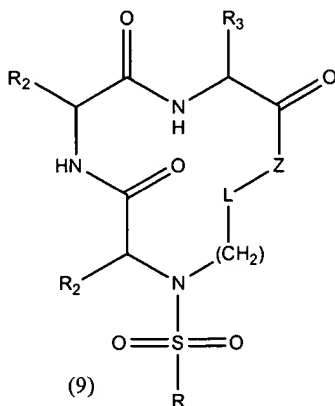
- - 25. (new) A macrocyclic compound according to claim 24, wherein said compound is of formula (8):

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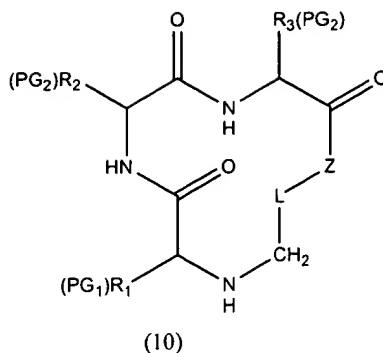
where L, Z, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as give in claim 24 and (PG<sub>1</sub>), (PG<sub>2</sub>) and (PG<sub>3</sub>) are protective groups for orthogonal protections in peptides synthesis. - -

- - 26. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (9):



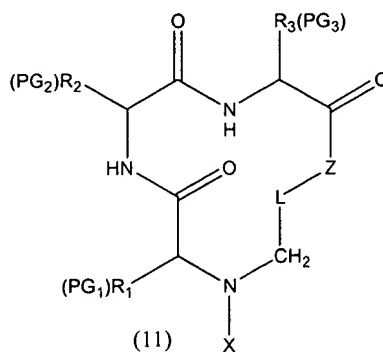
where L, Z, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as give in claim 24. - -

- - 27. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (10):



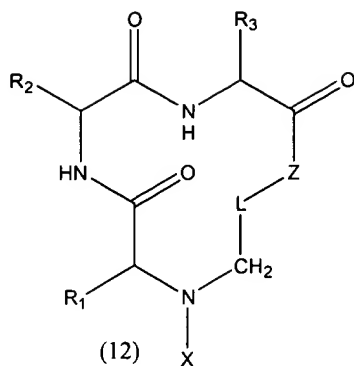
where L, Z, R,  $R_1$ ,  $R_2$  and  $R_3$  have the same meanings as give in claim 24 and  $(PG_1)$ ,  $(PG_2)$  and  $(PG_3)$  are protective groups for orthogonal protections in peptides synthesis. - -

- - 28. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (11):



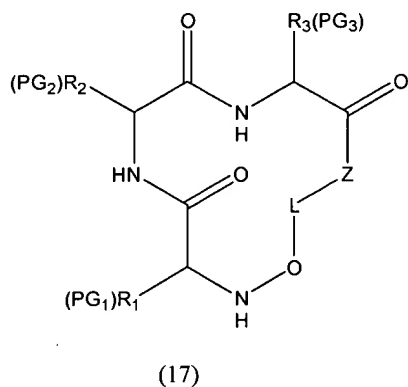
where L, Z, R,  $R_1$ ,  $R_2$  and  $R_3$  have the same meanings as give in claim 24 and  $(PG_1)$ ,  $(PG_2)$  and  $(PG_3)$  are protective groups for orthogonal protections in peptides synthesis. - -

- - 29. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (12):



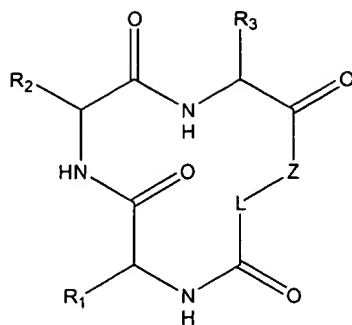
where L, Z, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as give in claim 24 and (PG<sub>1</sub>), (PG<sub>2</sub>) and (PG<sub>3</sub>) are protective groups for orthogonal protections in peptides synthesis. - -

- - 30. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (17):



where L, Z, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as give in claim 24 and (PG<sub>1</sub>), (PG<sub>2</sub>) and (PG<sub>3</sub>) are protective groups for orthogonal protections in peptides synthesis. - -

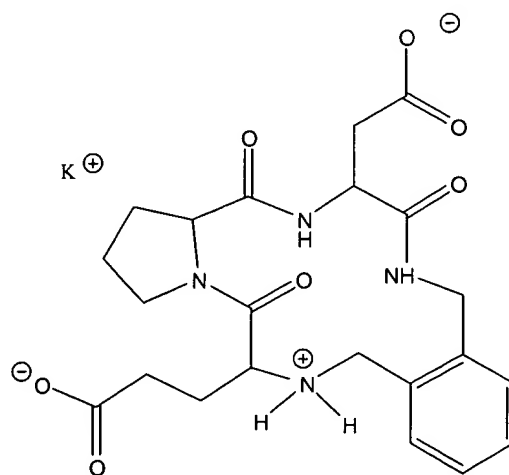
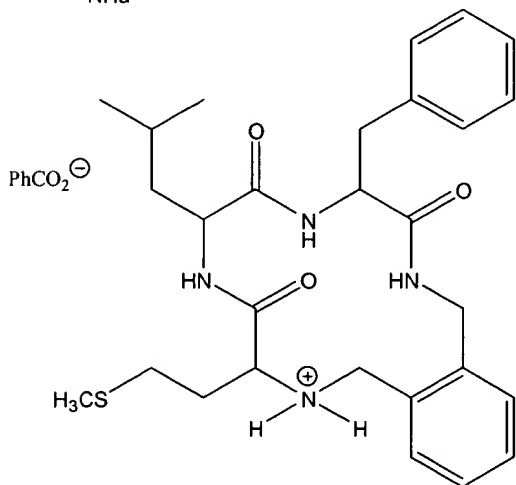
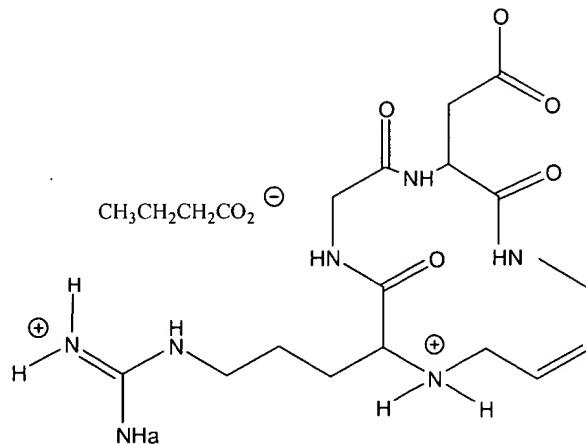
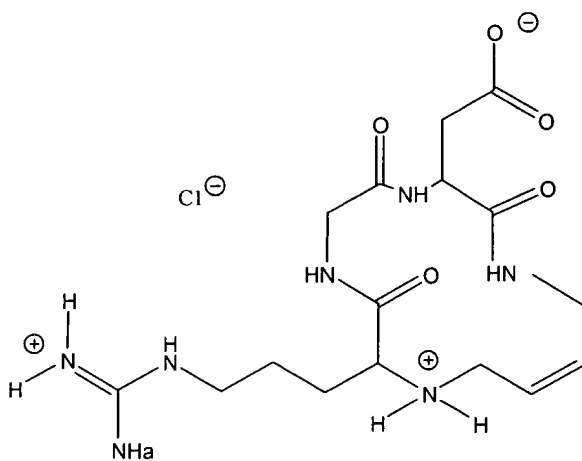
- - 31. (new) A macrocyclic compound according to claim 24, wherein said compound is of the formula (18):



(18)

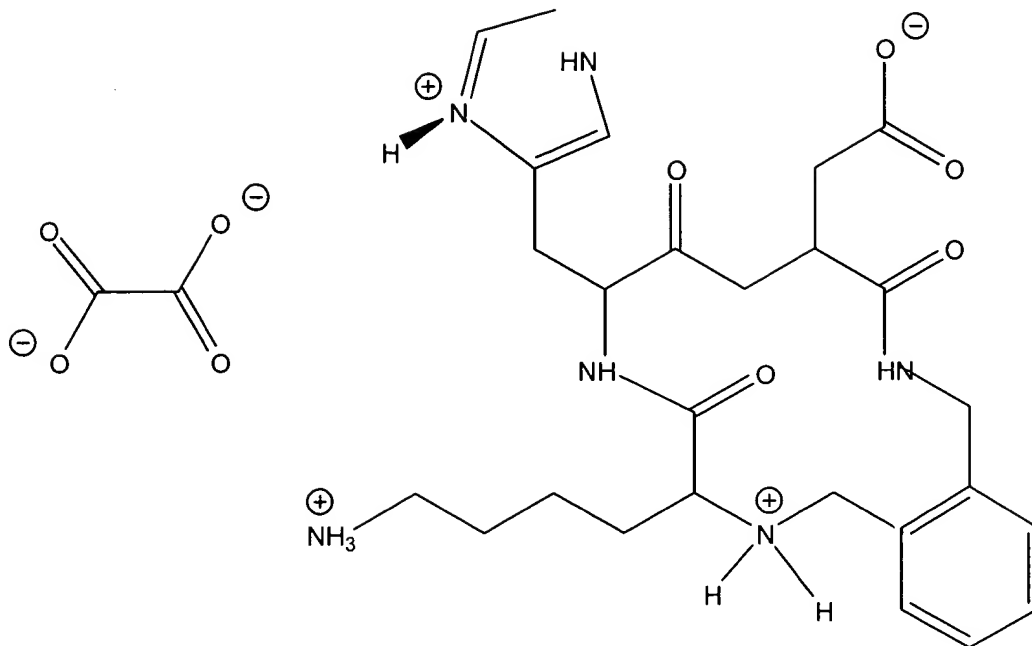
where L, Z, R, R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> have the same meanings as give in claim 24. - -

- - 32. (new) A macrocyclic compound according to claim 24, selected from the group consisting of:

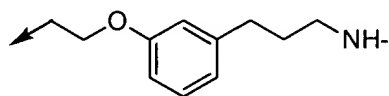
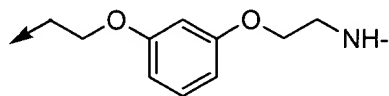
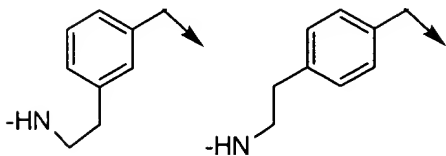
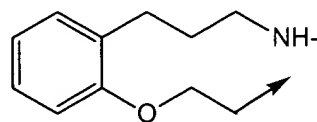
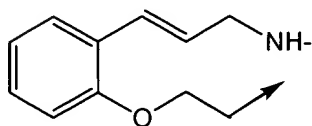
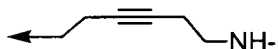
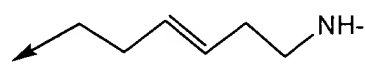
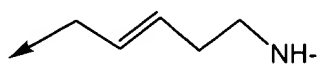
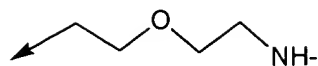




and



33. (new) The macrocyclic compound of claim 24 wherein part (T) is





corresponds to canceled claim 7. Claim 31 corresponds to canceled claim 8. Claim 32 corresponds to canceled claim 10.

The new claims are fully supported. Specifically, support for claim 24 can be found, for example, in claim 1 as originally filed; support for claim 25 can be found, for example, in claim 2 as originally filed; support for claim 26 can be found, for example, in claim 3 as originally filed; support for claim 27 can be found, for example, in claim 4 as originally filed; support for claim 28 can be found, for example, in claim 5 as originally filed; support for claim 29 can be found, for example, in claim 6 as originally filed; support for claim 30 can be found, for example, in claim 7 as originally filed; support for claim 31 can be found, for example, in claim 8 as originally filed; support for claim 32 can be found, for example, in claim 10 as originally filed; and support for claim 33 can be found, for example, in claim 1 as originally filed.

#### Inventorship

On July 15, 2002, Applicants requested deletion of Luc Quellet and Ruoxi Lan as inventors in this application. Such deletion results from the cancellation of claims 11-23. Applicants request confirmation from the Examiner that such deletion has been made.

#### Priority Claim

A certified copy the priority document Canadian application no. 2,284,459 (filed October 4, 1999) was submitted on January 22, 2003. Applicants request an acknowledgement from the Examiner in the next office action.

#### Objection

Claim 10 was objected to under 37 C.F.R. 1.75(c) as being improper dependent form for failing to further limit the subject matter of claim 1. Claim 1 has now been rewritten as new claim 24. Claim 24 specifies that d is an integer from 0 to 5 and e is an integer from 1 to 5. Claim 10 has now been rewritten as new claim 32. Claim 32 corresponds to claim 24 when d is set to 0. Hence, claim 32 properly depend from claim 24 and the objection has been overcome.

#### Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

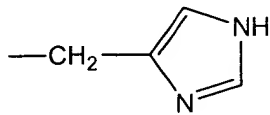
Claims 1-9 stand rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such as way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed.

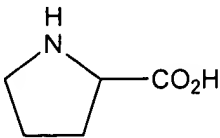
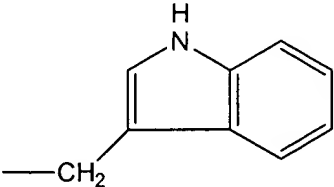
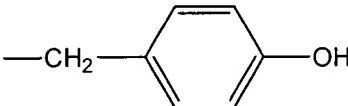
In contrast to canceled claim 1, new independent claim 24 is directed to (1) more limited amino acid building blocks and (2) more limited tether (T) component

(1) The Side Chains

The side chains are now limited to side chains of standard amino acids (Table 1), 4-hydroxyproline, and ornithine (Table 2).

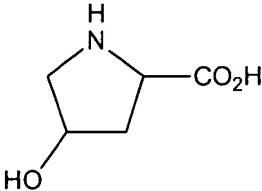
**Table 1: Standard amino acids and their side chains**

Amino Acid	Code	Side Chain (R <sub>AA</sub> )	Structure of side Chain (R <sub>AA</sub> )
Alanine	Ala, A	Methyl	-CH <sub>3</sub>
Arginine	Arg, A	Propylguanidino	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NHC(=NH)NH <sub>2</sub>
Asparagine	Asn, N	Methylcarboxamide	- CH <sub>2</sub> C(=O)NH <sub>2</sub>
Aspartic acid	Asp, D	Carboxymethyl	- CH <sub>2</sub> CO <sub>2</sub> H
Cysteine	Cys, C	Thiomethyl	- CH <sub>2</sub> SH
Gluatamic acid	Glu, E	Carboxyethyl	- CH <sub>2</sub> CH <sub>2</sub> -CO <sub>2</sub> H
Gluatamic	GLn, Q	Ethylcarboxamide	- CH <sub>2</sub> CH <sub>2</sub> C(=O)NH <sub>2</sub>
Glycine	Gly, G	None (Hydrogen)	-H
Histidine	His, H	3-Imidazolylmethyl	
Isoleucine	Ile, I	<i>sec</i> -Butyl	-CH(CH <sub>3</sub> )CH <sub>2</sub> CH <sub>3</sub>
Leucine	Leu, L	<i>iso</i> -Butyl	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>
Lysine	Lys, K	Aminobutyl	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>
Methionine	Met, M	Ethylthiomethyl	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>
Phenylalanine	Phe, F	Benzyl	-CH <sub>2</sub> Ph

Proline	Pro, P	Cyclic	
Serine	Ser, S	Hydroxymethyl	-CH <sub>2</sub> OH
Threonine	Thr, T	2-Hydroxymethyl	-CH(OH)CH <sub>3</sub>
Tryptophan	Trp, W	3-Indolylmethyl	
Tyrosine	Tyr, Y	4'-Hydroxybenzyl	
Valine	Val, V	Isopropyl	-CH(CH <sub>3</sub> ) <sub>2</sub>

\* When no stereochemistry is specifically indicated, the listing is meant to include both L and D enantiomers and, in the cases of Ile, Thr, and Hyp, all possible diastereoisomers.

**Table 2: Other Amino acids**

Amino Acid	Code	Side Chain (R <sub>AA</sub> )	Structure of side Chain (R <sub>AA</sub> )
4-Hydroxy-proline	Hyp	Cyclic	
Ornithine	Orn	Aminopropyl	-CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>

\* When no stereochemistry is specifically indicated, the listing is meant to include both L and D enantiomers and, in the cases of Ile, Thr, and Hyp, all possible diastereoisomers.

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Standard amino acid derivatives as well as their beta and gamma homologues are considered by those skilled in the art as within a reactant class. In particular, key points of reacting functionality, the amine and carboxylic acid moieties are the same in all members of the reactant class. Other functionalities on the side chains would be protected as is the standard practice in peptide chemistry and known to those skilled in the art.

(2) The Tether Component

The reacting functionalities are now limited to an alcohol or carboxylic acid on one end and an amine or alcohol on the other, so as to allow a general synthetic method to be successfully applied. Further, all of the claimed elements are related in that they utilize a multiple bond, ring or other functionality to limit conformational flexibility of the subsequent macrocyclic molecules. Each tether limits the type and number of low energy conformations that a cycle can occupy.

In summary, Applicants have significantly limited to the macrocyclic compound claim. The specification as filed provides sufficient written description to support the amended claims. That is to say, the specification contains all of the information that would be required by those skilled in the art to make and use the claimed inventions.

Rejection under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-10 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly not enabling for the vast majority of compounds that fall within the broad scope.

As discussed above, in the new claims 24-33, Applicants have significantly narrowed the scope of claims by limiting the choices of the amino acid side chain and the tether component.

One of skilled in the art would be able to use the compound of the present invention with known screening methods such as biological high throughput screening assays, and radioassays to identify compounds having antibacterial, antifungal, antiviral, antineoplastic or other pharmaceutical biological or chemical activity.

Hence, all pending claims are enabled.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-10 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants have corrected the missing bonds in the claims and in the specification.

Applicants have deleted the phrase "commonly used" from the claims.

Hence, all rejections have been overcome.

In view of the preceding amendments and remarks, Applicants submit that all rejections/objections have been overcome and that the application is now in condition for allowance.

Respectfully Submitted,

Date: March 10, 2003

By:

A handwritten signature in black ink, appearing to read "S. Peter Ludwig", written over a horizontal line.

S. Peter Ludwig  
Registration No. 25,351

Attorney for Applicant(s)

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